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## **Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asians With Nonvalvular Atrial Fibrillation**

### *A Network Meta-Analysis*

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# Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asians With Nonvalvular Atrial Fibrillation: A Network Meta-Analysis

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## Abstract

There are few head-to-head trials directly comparing non-vitamin K antagonist oral anticoagulants (NOACs) against one other. A network meta-analysis (NMA) was performed to examine the indirect comparisons among NOACs in Asians with nonvalvular atrial fibrillation (NVAF). STATA 15.0 and ADDIS 1.16.8 softwares were used to perform the statistical analysis. Odds ratios with 95% credible intervals were applied to evaluate the end points. The probabilities of treatment rank were used to understand which interventions are more effective and safe, and the total rank probability was 1. In our NMA, the rank probabilities of apixaban in the case of stroke or systemic embolism, death from any cause, major bleeding, and intracranial hemorrhage (ICH) were 0.47, 0.49, 0.42, and 0.51, respectively. For cases of myocardial infarction, the rank probabilities of rivaroxaban were 0.40. This NMA indirectly compares the main efficacy and safety end points among NOACs in Asians with NVAF, and the rank probability analysis showed that apixaban likely performs best in cases of stroke or systemic embolism, death from any cause, and ICH; rivaroxaban may have the best performance for myocardial infarction.

## Keywords

atrial fibrillation, Asian, NOACs, indirect comparison, network meta-analysis

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## Introduction

Patients with nonvalvular atrial fibrillation (NVAF) are at increased risk of stroke and death.<sup>1,2</sup> Warfarin, one of the Vitamin K antagonists, is an effective therapy in preventing stroke or systemic embolism for patients with NVAF.<sup>3-5</sup> However, there are some limitations for underuse of warfarin in clinical practice, such as a narrow therapeutic range and multiple interactions with food and drugs, requiring frequent laboratory coagulation monitoring and dose adjustments. Thus, several non-vitamin K antagonist oral anticoagulants (NOACs) have been developed and validated in large randomized trials, compared to warfarin.<sup>6-9</sup> All of the 4 NOACs have been confirmed to be superior or at least noninferior to warfarin in preventing stroke or systemic embolism, with lower rates of bleeding and mortality.<sup>6-9</sup>

Many studies have shown that warfarin is more underused in East Asia versus other regions of the world.<sup>10</sup> The effect of

NOACs in Asian NVAF populations has been recently evaluated, including a number of real-world studies.<sup>11-19</sup> In randomized trials, the NOACs appear to have greater efficacy and better safety in Asians compared to non-Asians.<sup>20</sup> The lower body weight and body mass index (BMI) in Chinese

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populations might be associated with the efficacy and safety of NOACs.<sup>21,22</sup>

Nevertheless, there are no head-to-head trials conducted to directly compare these NOACs against each other. An indirect comparison analysis on comparing the efficacy and safety of edoxaban to other agents has been recently published<sup>23</sup> but did not focus on Asian patients. In Asia, clinicians and patients are interested in identifying which of the NOACs performs better among Asian patients with NVAf. We performed a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of these 4 NOACs compared to each other, based on Asian data.

## Methods

### Inclusion and Exclusion Criteria

The following inclusion criteria were applied for selecting studies: (1) Types of studies: clinical studies focusing on the efficacy and safety of NOACs among Asian NVAf patients; (2) Participants: anticoagulated Asians with NVAf; and (3) Outcomes: (i) efficacy end points: stroke or systemic embolism, myocardial infarction, and death from any cause; (ii) safety end points: major bleeding defined according to the 2005 International Society on Thrombosis and Hemostasis criteria<sup>24</sup> and clinically relevant nonmajor bleeding. Studies with insufficient data (not describe the data of NOACs, respectively), those not published in English, and certain publication types (eg, conference, abstracts, letters, comments, case reports, and reviews) were excluded from this NMA.

### Literature Search

A comprehensive literature search of the PubMed, Elsevier, and Cochrane Library electronic databases was conducted by 2 independent reviewers (Qinmei Xiong and Cen Wang). The included studies were published from December 2010 to June 2019. Search terms included “atrial fibrillation,” “NOACs,” “dabigatran,” “apixaban,” “rivaroxaban,” and “edoxaban.” No research meeting the inclusion criteria was found in the manual search.

### Data Extraction and Quality Assessment of Individual Studies

Data extraction was performed independently by 2 reviewers based on the inclusion and exclusion criteria. Initial screening was conducted by reading titles and abstracts of all studies. Full texts of selected research articles were then reviewed to confirm if those studies met the inclusion criteria. Additionally, disagreements were resolved through discussion or consultation with a third reviewer (Kui Hong).

### Network Meta-Analysis and Statistical Analysis

Network meta-analysis was conducted to pool the results of direct and indirect comparisons using a Bayesian approach. All

data were analyzed using STATA 15.0 and ADDIS (Aggregate Data Drug Information System) 1.16.8 software (Drug Information Systems, Groningen, the Netherlands). We first performed a pairwise meta-analysis to directly evaluate the treatment effect of NOACs. The odds ratio (OR) with a 95% confidence interval (CI) was applied to evaluate the end points. For the NMA, ORs with 95% credible intervals (CrIs) were used. Moreover, a consistency model based on the Markov chain Monte Carlo simulation method was applied by using 50 000 simulation iterations for each 4 chains with a burn-in period of the first 20 000 iterations. Node-splitting analysis and inconsistency standard deviation (ISD) were then performed to evaluate the consistency of the data. When the *P* value of the node-splitting analysis was  $>.05$  and the 95% CI of the ISD contained 1, the consistency model was selected.<sup>25</sup> Convergence was evaluated using potential scale reduction factor (PSRF) and the Brooks-Gelman-Rubin method, and a value of  $\sim 1$  represented good convergence. Value of  $P < .05$  was regarded as a statistically significant result. We could also use the probabilities of treatment rankings to understand which interventions are more effective and safe; the total rank probability was 1. According to our pooled result, Rank 1 was the worst and Rank N was the best.

## Results

### Flow Diagram of Literature Search

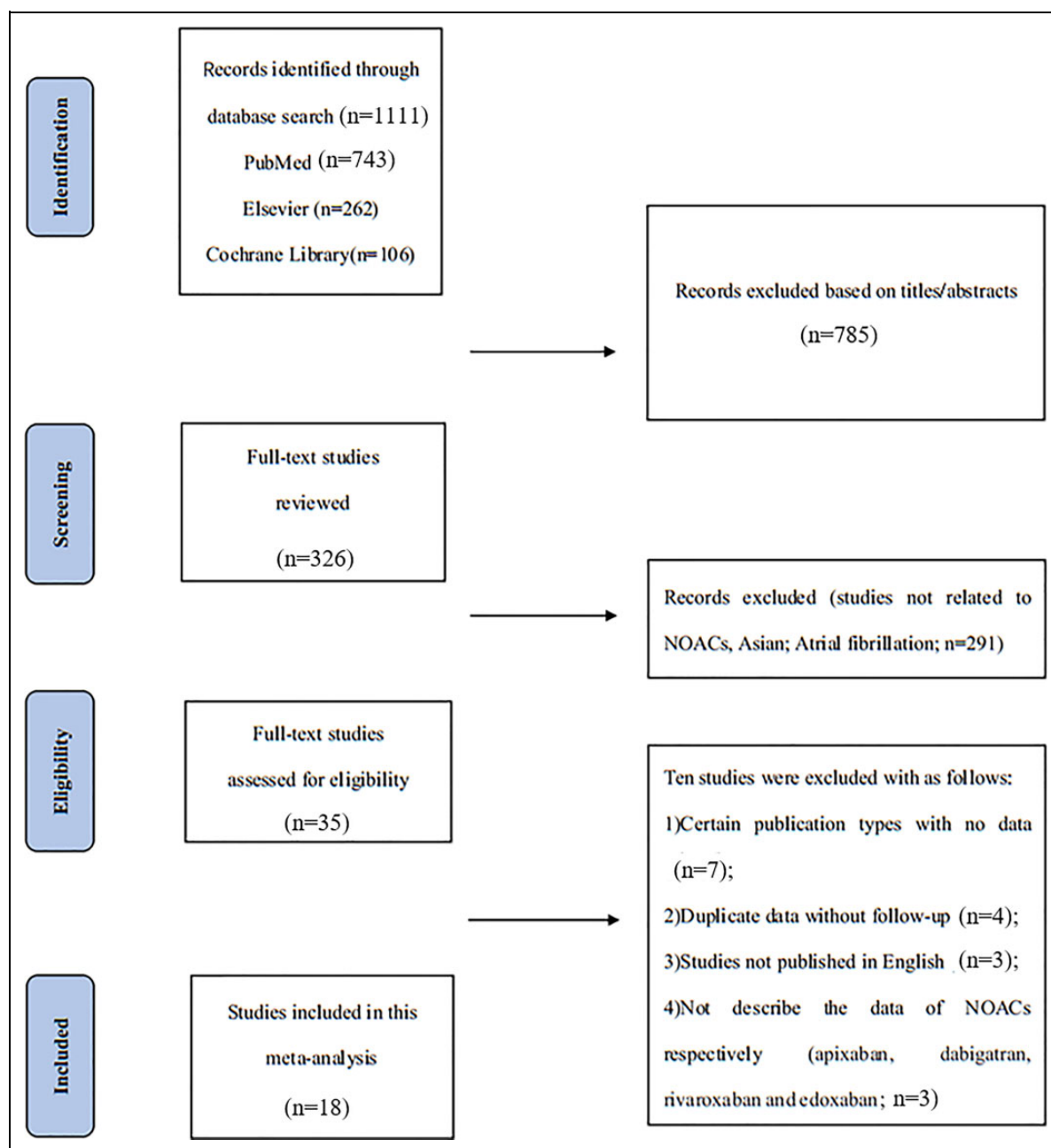
Using the above-mentioned search strategies, we found a total of 1111 studies (743 in PubMed, 262 in Elsevier, 106 in Cochrane Library). We excluded 785 studies by reading the titles and abstracts. When we screened the full texts, 291 studies were eliminated because these studies did not relate to NOACs, Asian populations, and atrial fibrillation. Finally, 18 studies were included. The other studies were excluded for the following reasons: (1) certain publication types with no data ( $n = 7$ ); (2) duplicate data without follow-up ( $n = 4$ ); (3) studies not published in English ( $n = 3$ ); and (4) studies not describing NOACs (apixaban, dabigatran, rivaroxaban, and edoxaban;  $n = 3$ ; Figure 1).

### Characteristics of the Included Studies and Patients

All 18 included studies were conducted in China,<sup>12,13,15,18,26-28</sup> Singapore,<sup>12,15,19</sup> Korea,<sup>12-15,17-19,29</sup> Japan,<sup>12,13,15,30,31</sup> India<sup>12</sup>, Malaysia,<sup>11,12,15,16,32</sup> the Philippines,<sup>12,15</sup> Turkey,<sup>33</sup> Israel,<sup>34</sup> or Thailand.<sup>12</sup> A total of 71 227 anticoagulated patients with NVAf were studied. The oral anticoagulants were warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban (Table 1).

### Pairwise Meta-Analysis

The risk of stroke or systemic embolism was decreased by 60% and 55% for patients who took dabigatran and rivaroxaban, respectively, when compared to those who took warfarin (dabigatran vs warfarin [OR = 0.4; 95% CI: 0.26-0.6] and rivaroxaban vs warfarin [OR = 0.45; 95% CI: 0.28-0.72]). For death



**Figure 1.** Flow diagram of literature search.

from any cause risk, the risk was decreased by 63% and 66% for patients who took rivaroxaban and dabigatran when compared to those who took warfarin (rivaroxaban vs warfarin: OR = 0.37; 95% CI: 0.21-0.67; dabigatran vs warfarin: OR = 0.34, 95% CI: 0.13-0.91). When compared to those who took warfarin, intracranial hemorrhage (ICH) was decreased by 81%, 67%, and 76% among patients who took apixaban, dabigatran, or rivaroxaban, respectively (apixaban vs warfarin: OR = 0.19, 95% CI: 0.05-0.72; dabigatran vs warfarin: OR = 0.33, 95% CI: 0.2-0.54; rivaroxaban vs warfarin: OR = 0.24, 95% CI: 0.18-0.33). No significant difference was found for myocardial infarction and major bleeding (Figure 2).

### Network Meta-Analysis

In our NMA, the indirect comparisons of the NOACs were based on the published direct comparisons with the NOACs against warfarin. The data for this section were consistent with the pairwise meta-analysis. In node-splitting analysis, all of the *P* values were over .05, with the 95% CI of the ISD containing 1 and all of the PSRFs ranging from 1.00 to 1.01. This indicated that all included studies had good consistence, and the model obtained good convergence. Therefore, the consistency model was selected.

The indirect comparisons of all of the end points for the oral anticoagulants are shown in (Supplemental Table 1). There are

**Table 1.** Summary of Patients' Characteristics in 18 Included Studies.

Study	Country	Follow-Up, months	Study Arms	N	Drug	End Points
Chung et al (2011) <sup>19</sup>	Korea, Singapore	12	2	235	E/V	Major bleeding
Hori et al (2013) <sup>12</sup>	China, Japan, Korea, India, Malaysia, Philippines, Singapore, Thailand	24	2	2782	D/V	Stroke/SE; MI; Death; Major bleeding; ICH
Wong et al (2014) <sup>18</sup>	China, Korea	22	2	932	R/V	Stroke/SE; MI; Death; Major bleeding; ICH
Goto et al (2014) <sup>15</sup>	China, Japan, Korea, Philippines, Malaysia, Singapore	20	2	1993	A/V	Stroke/SE; MI; Death; Major bleeding; ICH
Yap et al (2016) <sup>11</sup>	Malaysia	20	2	1000	D/V	Stroke/SE; Major bleeding; ICH
Yamashita et al (2016) <sup>13</sup>	Japan, China, Korea	24	2	1943	E/V	Stroke/SE; MI; Death; Major bleeding; ICH
Cha et al (2017) <sup>14</sup>	Korea	24	4	34 833	A/D/R/V	Stroke/SE; Death; ICH
Lee et al (2017) <sup>17</sup>	Korea	24	2	1098	D/V	Stroke/SE; MI; Death; Major bleeding; ICH
Beshir et al (2018) <sup>16</sup>	Malaysia	12	3	1017	D/R/V	Major bleeding
Jeong et al (2019) <sup>29</sup>	South Korea	12	2	1608	R/V	Stroke/SE; MI; Death; Major bleeding; ICH
Mao et al (2014) <sup>28</sup>	China	18	2	353	R/V	Stroke/SE; major bleeding; ICH
Yamashita et al (2012) <sup>31</sup>	Japan	12	2	519	E/V	Major bleeding
Yap et al (2017) <sup>32</sup>	Malaysia	93	2	200	D/V	Stroke/SE; ICH
Naganuma et al (2017) <sup>30</sup>	Japan	10	2	362	D/V	Stroke/SE; Major bleeding
Li et al (2017) <sup>26</sup>	China	22	3	2099	D/R/V	Stroke/SE; ICH
Ho et al (2015) <sup>27</sup>	China	36	2	1821	D/V	Stroke/SE; Death; ICH
Yiginer et al (2016) <sup>33</sup>	Turkey	17	2	183	D/R	Death; Major bleeding; ICH
Ellis et al (2016) <sup>34</sup>	Israel	8	3	18 249	D/R/V	ICH

Abbreviations: SE, systemic embolism; MI, myocardial infarction; ICH, intracranial hemorrhage; V, vitamin-K antagonists (Warfarin); A, apixaban; D, dabigatran; R, rivaroxaban.

13 studies providing data on 15 direct comparisons between 4 different treatment nodes for major bleeding, 13 studies providing data on 20 direct comparisons between 4 different treatment nodes for stroke or systemic embolism, 13 studies providing data on 21 direct comparisons between 4 different treatment nodes for intracranial bleeding, 9 studies providing data on 14 direct comparisons between 4 different treatment nodes for death from any cause, and 6 studies providing data on 6 direct comparisons between 4 different treatment nodes for myocardial infarction (Figure 3). All the results of the NMA were consistent with the pairwise meta-analysis, but there were no significant differences among the NOACs in the 5 end points (Supplemental Table 1).

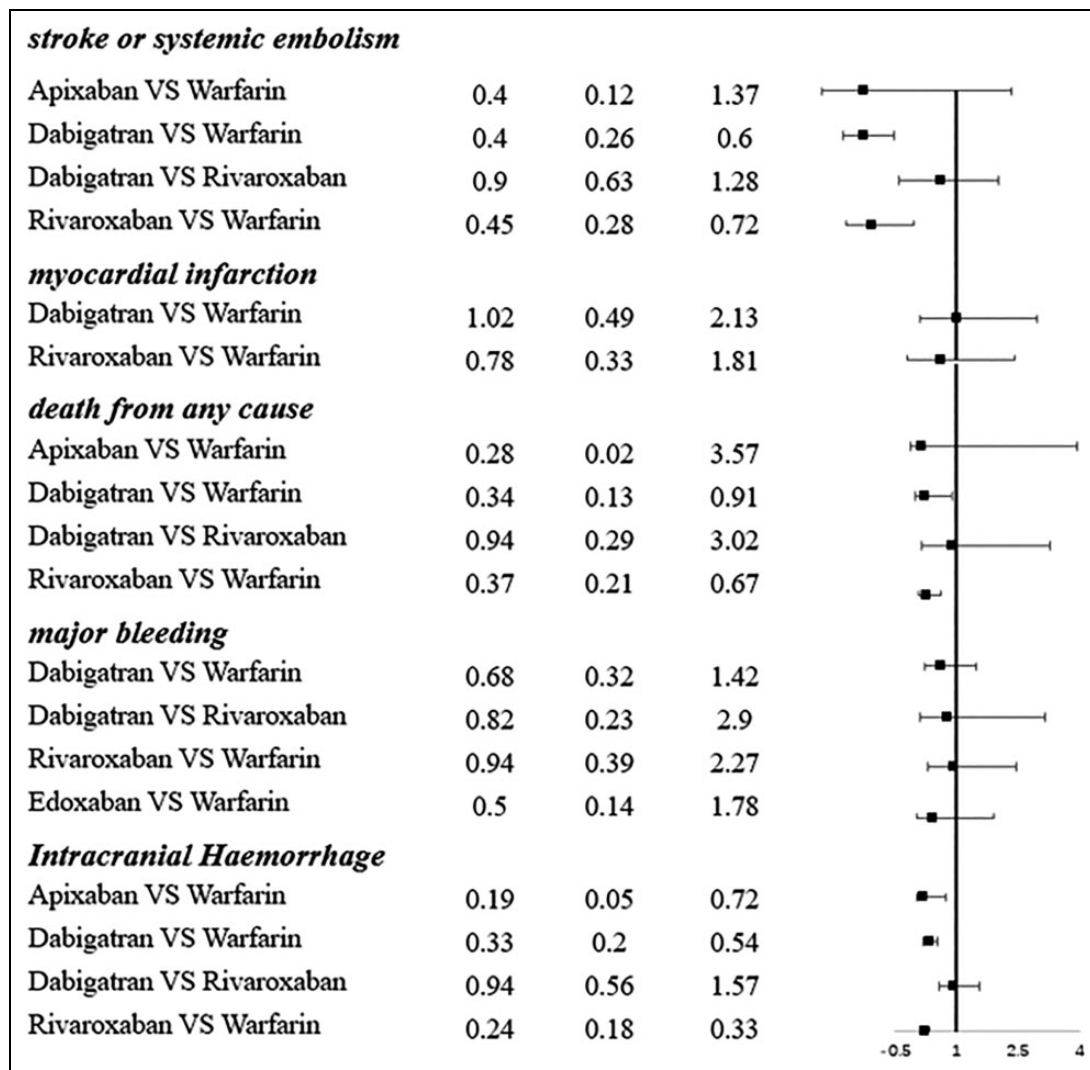
Although no significant differences were shown for all of the selected end points in the NMA, the rank probability of the 5 oral anticoagulants showed the degree of drug efficacy in each end point, which may provide guidance for medical decision-making in clinical practice. Apixaban likely has the most effective drug for the prevention of stroke or systemic embolism, death from any cause, major bleeding, and ICH, with rank probabilities of 0.47, 0.49, 0.42, and 0.51, respectively. For cases of myocardial infarction, rivaroxaban may be considered as the best drug, with ranking probabilities of 0.40 (Supplemental Figure 1).

## Discussion

Our pairwise meta-analysis has demonstrated that dabigatran and rivaroxaban performed better than warfarin in cases of

stroke or systemic embolism and death from any cause; apixaban, dabigatran, and rivaroxaban had a lower risk of ICH compared to warfarin. In our NMA, the ORs with 95% CrIs demonstrated no significant differences among the NOACs. Rank probability analysis showed that apixaban may have the highest efficacy for stroke or systemic embolism, death from any cause, major bleeding, and ICH; rivaroxaban may have the best performance for myocardial infarction. As far as we are aware, this is the first NMA comparing NOACs that is focused on Asian patients with NVAF.

The pairwise meta-analysis in Asians was generally consistent with previous studies. In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, for example, dabigatran was superior to warfarin for stroke or systemic embolism, myocardial infarction, major bleeding, and intracranial bleeding.<sup>7</sup> In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial, rivaroxaban had a lower risk of ICH when compared to warfarin.<sup>9</sup> In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, apixaban was superior to warfarin for stroke or systemic embolism, death from any cause, major bleeding, and intracranial bleeding.<sup>6</sup> In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis in Myocardial Infarction 48 trial, edoxaban had a lower risk of death from any cause, major bleeding, and ICH when compared to warfarin.<sup>8</sup> Unfortunately, these 4 studies did not directly evaluate the differences in efficacy and safety comparing those NOACs to one another.



**Figure 2.** Pairwise meta-analysis results for 5 oral anticoagulants in 5 end points.

Cha et al<sup>14</sup> reported that rivaroxaban had a 1.94-fold elevated risk of stroke or systemic embolism when compared to apixaban (rivaroxaban vs apixaban: OR = 1.94; 95% CI: 1.01-3.71). In the death from any cause, dabigatran and rivaroxaban had a 2.22- and 3.83-fold elevated risk when compared to apixaban, respectively (dabigatran vs apixaban: OR = 2.22, 95% CI: 1.20-4.10; rivaroxaban vs apixaban: OR = 3.83, 95% CI: 2.16-6.79), and rivaroxaban has a 1.72-fold elevated risk when compared to dabigatran (rivaroxaban vs dabigatran: OR = 1.72, 95% CI: 1.24-2.40).

Body weight and BMI in Asians have been found to be lower than in white populations in many studies.<sup>21,22</sup> Low body weight ( $\leq 60$  kg) is an important covariate for bleeding, and Cha et al reported that being underweight increases the risk of major bleeding and all-cause death when compared to being normal weight or overweight.<sup>14</sup>

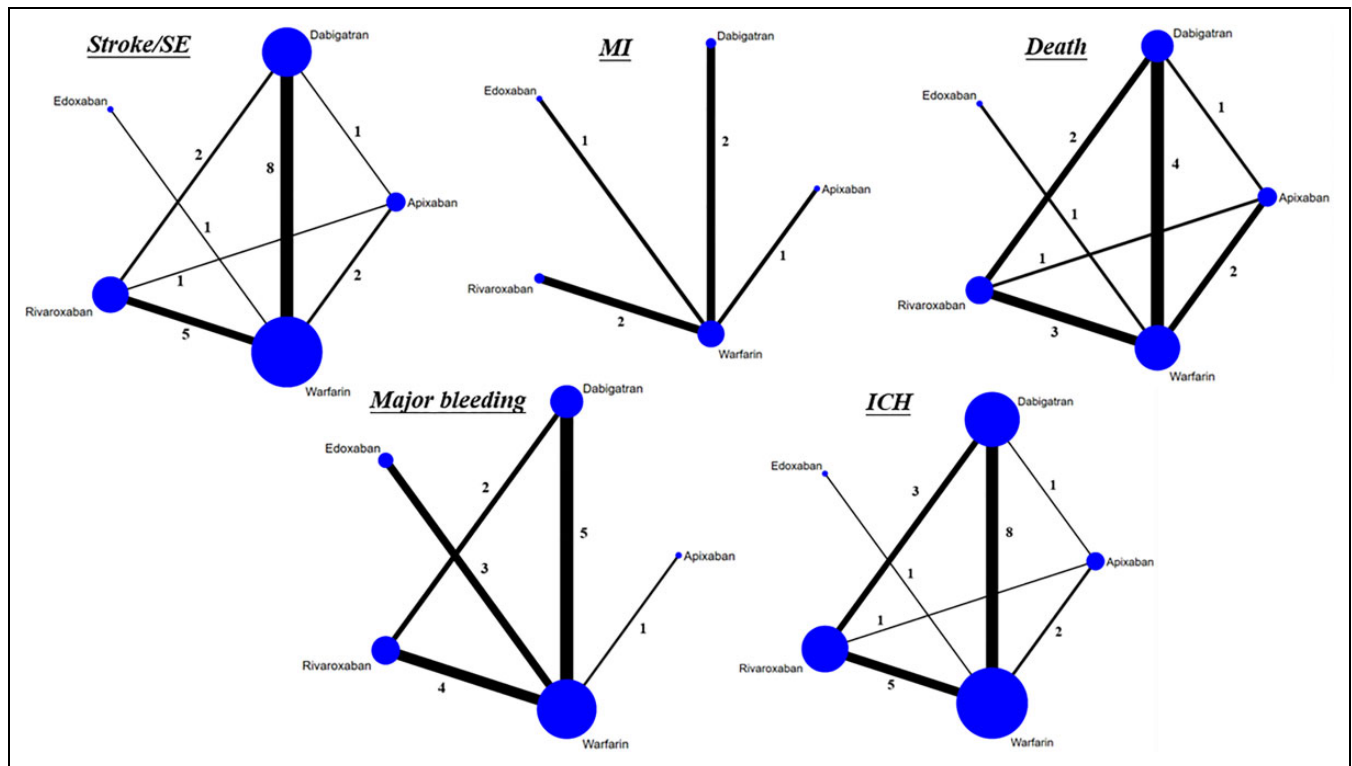
Indeed, Asians may have a propensity for bleeding events when taking warfarin.<sup>12</sup> For example, a previous study showed that Asian patients with AF treated with warfarin had a 4-fold higher hazard ratio (HR) for ICH when compared to whites.<sup>22</sup>

In a recent meta-analysis, the incidence of ICH was approximately 2-fold higher in Asians compared to whites.<sup>35</sup> Additionally, the salt sensitivity of different ethnic groups may be related to ICHs.<sup>36</sup> Because more Asian patients with AF had ICH than did non-Asians, the developing countries appear to have 80% of the global burden of ICH.<sup>37</sup>

Several studies have demonstrated that patients with AF used NOACs to reduce the risk of bleeding.<sup>38,39</sup> In our pairwise meta-analysis, apixaban, dabigatran, and rivaroxaban had a lower risk than warfarin for ICH. In our NMA, the ORs with 95% CrIs demonstrated no significant differences among the NOACs, but the rank probability analysis showed that apixaban had the highest probability of performing the best among all anticoagulants for ICH.

### Limitations

As an indirect comparison analysis, the present NMA has some inherent limitations. We found only 5 head-to-head studies on NOACs, and the 5 studies were conducted in China,<sup>26</sup>



**Figure 3.** Network of the included comparisons.

Malaysia,<sup>16</sup> Israel,<sup>34</sup> and Korea.<sup>14</sup> More direct comparisons should be performed as the findings of indirect comparisons can only be considered as guidance for clinical practice. Moreover, heterogeneity for clinical, methodological, and statistical limitations always exists.

## Conclusion

In our NMA, to indirectly compare the main efficacy and safety end points among NOACs in Asians with NVAF, there were no significant differences among the NOACs for efficacy, but rank probability analysis showed that apixaban probably performs best in stroke or systemic embolism, death from any cause, major bleeding, and ICH. For cases of myocardial infarction, rivaroxaban may be considered as the best drug.

## Authors' Note

Gregory Y. H. Lip and Kui Hong are co-senior authors. Qinmei Xiong, Cen Wang, and Hualong Liu are co-first authors.

## Declaration of Conflicting Interests

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## Supplemental Material

Supplemental material for this article is available online.

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